DESCRIPTION

RIBOZYME TREATMENT OF DISEASES OR CONDITIONS RELATED TO LEVELS OF NF-κB

Related Applications

This application is a continuation-in-part of Stinchcomb et al., "Method and Composition for Treatment of Restenosis and Cancer Using Ribozymes," filed May 18, 1994, U.S.S.N. 08/245,466 which is a continuation-in-part of Draper, "Method and Reagent for Treatment of a Stenotic Condition", filed December 7, 1992, U.S. Serial No. 07/987,132, both hereby incorporated by reference herein.

Field of the Invention

The present invention relates to therapeutic compositions and methods for the treatment or diagnosis of diseases or conditions related to NF-κB levels, such as restenosis, rheumatoid arthritis, asthma, inflammatory or autoimmune disorders and transplant rejection.

Background Of The Invention

The following is a brief description of the physiological role of NF-κB. The discussion is not meant to be complete and is provided only for understanding of the invention that follows. This summary is not an admission that any of the work described below is prior art to the claimed invention.

The nuclear DNA-binding activity, NF-κB, was first identified as a factor that binds and activates the immunoglobulin κ light chain enhancer in B cells. NF-κB now is known to activate transcription of a variety of other cellular genes (*e.g.*, cytokines, adhesion proteins, oncogenes and viral proteins) in response to a variety of stimuli (*e.g.*, phorbol esters, mitogens, cytokines and oxidative stress). In addition, molecular and biochemical characterization of NF-κB has shown that the activity is due to a homodimer or heterodimer of a family of DNA binding subunits. Each subunit bears a stretch of 300 amino acids that is homologous to the oncogene, v-*rel*. The activity first described as NF-κB is a heterodimer of

p49 or p50 with p65. The p49 and p50 subunits of NF–κB (encoded by the nf-κB2 or nf–κB1 genes, respectively) are generated from the precursors NF–κB1 (p105) or NF–κB2 (p100). The p65 subunit of NF–κB (now termed Rel A) is encoded by the *rel* A locus.

The roles of each specific transcription-activating complex now are being elucidated in cells (N.D. Perkins, et al., 1992 Proc. Natl Acad. Sci USA 89, 1529-1533). For instance, the heterodimer of NF–κB1 and Rel A (p50/p65) activates transcription of the promoter for the adhesion molecule, VCAM-1, while NF–κB2/RelA heterodimers (p49/p65) actually inhibit transcription (H.B. Shu, et al., Mol. Cell. Biol. 13, 6283-6289 (1993)). Conversely, heterodimers of NF–κB2/RelA (p49/p65) act with Tat-I to activate transcription of the HIV genome, while NF–κB1/RelA (p50/p65) heterodimers have little effect (J. Liu, N.D. Perkins, R.M. Schmid, G.J. Nabel, J. Virol. 1992 66, 3883-3887). Similarly, blocking *rel* A gene expression with antisense oligonucleotides specifically blocks embryonic stem cell adhesion; blocking NF–κB1 gene expression with antisense oligonucleotides had no effect on cellular adhesion (Narayanan et al., 1993 Mol. Cell. Biol. 13, 3802-3810). Thus, the promiscuous role initially assigned to NF–κB in transcriptional activation (M.J. Lenardo, D. Baltimore, 1989 Cell 58, 227-229) represents the sum of the activities of the rel family of DNA-binding proteins. This conclusion is supported by recent transgenic "knock-out" mice of individual members of the *rel* family. Such "knock-outs" show few developmental defects, suggesting that essential transcriptional activation functions can be performed by more than one member of the rel family.

A number of specific inhibitors of NF–κB function in cells exist, including treatment with phosphorothioate antisense oligonucleotide, treatment with double-stranded NF–κB binding sites, and over expression of the natural inhibitor MAD-3 (an IκB family member). These agents have been used to show that NF–κB is required for induction of a number of molecules involved in inflammation, as described below.

•NF–κB is required for phorbol ester-mediated induction of IL-6 (I. Kitajima, et al., Science 258, 1792-5 (1992)) and IL-8 (Kunsch and Rosen, 1993 Mol. Cell. Biol. 13, 6137-46).

•NF–κB is required for induction of the adhesion molecules ICAM-1 (Eck, et al., 1993 Mol. Cell. Biol. 13, 6530-6536), VCAM-1 (Shu et al., *supra*), and E-selectin (Read, et al., 1994 J. Exp. Med. 179, 503-512) on endothelial cells.

•NF–κB is involved in the induction of the integrin subunit, CD18, and other adhesive properties of leukocytes (Eck et al., 1993 *supra*).

The above studies suggest that NF–κB is integrally involved in the induction of cytokines and adhesion molecules by inflammatory mediators. Two recent papers point to another connection between NF–κB and inflammation: glucocorticoids may exert their anti-inflammatory effects by inhibiting NF–κB. The glucocorticoid receptor and p65 both act at NF–κB binding sites in the ICAM-1 promoter (van de Stolpe, et al., 1994 J. Biol. Chem. 269, 6185-6192). Glucocorticoid receptor inhibits NF–κB-mediated induction of IL-6 (Ray and Prefontaine, 1994 Proc. Natl Acad. Sci USA 91, 752-756). Conversely, overexpression of p65 inhibits glucocorticoid induction of the mouse mammary tumor virus promoter. Finally, protein cross-linking and co-immunoprecipitation experiments demonstrated direct physical interaction between p65 and the glucocorticoid receptor (*Id.*).

Summary of the Invention

This invention relates to ribozymes, or enzymatic RNA molecules, directed to cleave mRNA species encoding Rel A protein (p65). In particular, applicant describes the selection and function of ribozymes capable of cleaving this RNA and their use to reduce activity of NF–κB in various tissues to treat the diseases discussed herein. Such ribozymes are also useful for diagnostic applications.

Ribozymes that cleave *rel A* mRNA represent a novel therapeutic approach to inflammatory or autoimmune disorders. Antisense DNA molecules have been described that block NF–κB activity. See Narayanan *et al., supra.* However, ribozymes may show greater perdurance or lower effective doses than antisense molecules due to their catalytic properties and their inherent secondary and tertiary structures. Such ribozymes, with their catalytic activity and increased site specificity (as described below), represent more potent and safe therapeutic molecules than antisense oligonucleotides.

Applicant indicates that these ribozymes are able to inhibit the activity of NF–κB and that the catalytic activity of the ribozymes is required for their inhibitory effect. Those of ordinary skill in the art, will find that it is clear from the examples described that other ribozymes that cleave *rel A* encoding mRNAs may be readily designed and are within the invention.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in *trans* (and thus can cleave other RNA molecules) under physiological conditions. Table I summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over other technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf, T. M., et al., 1992, Proc. Natl. Acad. Sci. USA, **89**, 7305-7309). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

In preferred embodiments of this invention, the enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but may also be formed in the motif of a hepatitis delta virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or *Neurospora* VS RNA. Examples of such hammerhead motifs are described by Rossi *et al.*, 1992, *Aids Research and Human Retroviruses*, **8**, 183, of hairpin motifs by Hampel *et al.*, "RNA Catalyst for Cleaving Specific RNA Sequences," filed September 20, 1989, which is a continuation-in-part of U.S. Serial No. 07/247,100 filed September 20, 1988, Hampel and Tritz, 1989, *Biochemistry*, **28**, 4929, and Hampel *et al.*, 1990, *Nucleic Acids Res.earch*, **18**,299, and an example of the hepatitis delta virus motif is described by Perrotta and Been, 1992, *Biochemistry*, **31**, 16, of the RNaseP motif by Guerrier-Takada et al., 1983,*Cell*, **35**, 849, *Neurospora* VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990 *Cell* 61, 685-696; Saville and Collins, 1991 Proc. Natl. Acad. Sci. USA 88, 8826-8830; Collins and Olive, 1993 Biochemistry 32, 2795-2799) and of the Group I intron by Cech et al., U.S. Patent 4,987,071. These specific motifs are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule.

The invention provides a method for producing a class of enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target Rel A encoding mRNA such that specific treatment of a disease or condition can be provided with either one or several enzymatic nucleic acids. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA vectors that are delivered to specific cells.

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) are used for

exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. However, these catalytic RNA molecules can also be expressed within cells from eukaryotic promoters (e.g., Scanlon, K. J., et al., 1991, *Proc. Natl. Acad. Sci. USA*, **88**, 10591-5; Kashani-Sabet, M., et al., 1992, *Antisense Res. Dev.*, **2**, 3-15; Dropulic, B., et al., 1992, *J Virol*, **66**, 1432-41; Weerasinghe, M., et al., 1991, *J Virol*, **65**, 5531-4; Ojwang, J. O., et al., 1992, *Proc. Natl. Acad. Sci. USA* , **89**, 10802-6; Chen, C. J., et al., 1992, *Nucleic Acids Res.*, **20**, 4581-9; Sarver, H., et al., 1990, *Science*, **247**, 1222-1225)). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Draper et al., PCT WO93/23569, and Sullivan et al., PCT WO94/02595, both hereby incorporated in their totality by reference herein; Ohkawa, J., et al., 1992, *Nucleic Acids Symp. Ser.*, **27**, 15-6; Taira, K., et al., 1991, *Nucleic Acids Res.*, **19**, 5125-30; Ventura, M., et al., 1993, *Nucleic Acids Res.*, **21**, 3249-55) .

Inflammatory mediators such as lipopolysaccharide (LPS), interleukin-1 (IL-1) or tumor necrosis factor-a (TNF-α) act on cells by inducing transcription of a number of secondary mediators, including other cytokines and adhesion molecules. In many cases, this gene activation is known to be mediated by the transcriptional regulator, NF-κB. One subunit of NF-κB, the *rel*A gene product (termed RelA or p65) is implicated specifically in the induction of inflammatory responses. Ribozyme therapy, due to its exquisite specificity, is particularly well-suited to target intracellular factors that contribute to disease pathology. Thus, ribozymes that cleave mRNA encoded by *rel* A may represent novel therapeutics for the treatment of inflammatory and autoimmune disorders.

Thus, in a first aspect, the invention features ribozymes that inhibit RelA production. These chemically or enzymatically synthesized RNA molecules contain substrate binding domains that bind to accessible regions of their target mRNAs. The RNA molecules also contain domains that catalyze the cleavage of RNA. The RNA molecules are preferably ribozymes of the hammerhead or hairpin motif. Upon binding, the ribozymes cleave the target RelA encoding mRNAs, preventing translation

and p65 protein accumulation. In the absence of the expression of the target gene, a therapeutic effect may be observed.

By "inhibit" is meant that the activity or level of RelA encoding mRNA is reduced below that observed in the absense of the ribozyme, and preferably is below that level observed in the presence of an inactive RNA molecule able to bind to the same site on the mRNA, but unable to cleave that RNA.

Such ribozymes are useful for the prevention of the diseases and conditions discussed above, and any other diseases or conditions that are related to the level of NF–κB activity in a cell or tissue. By "related" is meant that the inhibition of *rel*A mRNA and thus reduction in the level of NF–κB activity will relieve to some extent the symptoms of the disease or condition.

Ribozymes are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection or the use of a catheter, infusion pump or stent, with or without their incorporation in biopolymers. In preferred embodiments, the ribozymes have binding arms which are complementary to the sequences in Tables II, III, VI - VII. Examples of such ribozymes are shown in Tables IV - VII. Examples of such ribozymes consist essentially of sequences defined in these Tables. By "consists essentially of" is meant that the active ribozyme contains an enzymatic center equivalent to those in the examples, and binding arms able to bind mRNA such that cleavage at the target site occurs. Other sequences may be present which do not interfere with such cleavage.

In another aspect of the invention, ribozymes that cleave target molecules and inhibit NF–κB activity are expressed from transcription units inserted into DNA, RNA, or viral vectors. Preferably, the recombinant vectors capable of expressing the ribozymes are locally delivered as described above, and transiently persist in target cells. Once expressed, the ribozymes cleave the target mRNA. The recombinant vectors are preferably DNA plasmids or adenovirus vectors. However, other mammalian cell vectors that direct the expression of RNA may be used for this purpose.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description Of The Preferred Embodiments

The drawings will first briefly be described.

Drawings:

Figure 1 is a diagrammatic representation of the hammerhead ribozyme domain known in the art.

Figure 2a is a diagrammatic representation of the hammerhead ribozyme domain known in the art; Figure 2b is a diagrammatic representation of the hammerhead ribozyme as divided by Uhlenbeck (1987, *Nature*, **327**, 596-600) into a substrate and enzyme portion; Figure 2c is a similar diagram showing the hammerhead divided by Haseloff and Gerlach (1988, *Nature* , **334**, 585-591) into two portions; and Figure 2d is a similar diagram showing the hammerhead divided by Jeffries and Symons (1989, *Nucl. Acids. Res.*, **17**, 1371-1371) into two portions.

Figure 3 is a representation of the general structure of the hairpin ribozyme domain known in the art.

Figure 4 is a representation of the general structure of the hepatitis delta virus ribozyme domain known in the art.

Figure 5 is a representation of the general structure of the VS RNA ribozyme domain known in the art.

Figure 6 is a schematic representation of an RNAseH accessibility assay. Specifically, the left side of Figure 6 is a diagram of complementary DNA oligonucleotides bound to accessible sites on the target RNA. Complementary DNA oligonucleotides are represented by broad lines labeled A, B, and C. Target RNA is represented by the thin, twisted line. The right side of Figure 6 is a schematic of a gel separation of uncut target RNA from a cleaved target RNA. Detection of target RNA is by autoradiography of body-labeled, T7 transcript. The bands common to

each lane represent uncleaved target RNA; the bands unique to each lane represent the cleaved products.

Ribozymes

Ribozymes of this invention block to some extent NF-κB expression and can be used to treat disease or diagnose such disease. Ribozymes will be delivered to cells in culture and to cells or tissues in animal models of restenosis, transplant rejection and rheumatoid arthritis. Ribozyme cleavage of *relA* mRNA in these systems may prevent inflammatory cell function and alleviate disease symptoms.

Target sites

Targets for useful ribozymes can be determined as disclosed in Draper et al supra, Sullivan *et al.*, supra, as well as by Draper et al., "Method and reagent for treatment of arthritic conditions U.S.S.N. 08/152,487, filed 11/12/93, and hereby incorporated by reference herein in totality. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Ribozymes to such targets are designed as described in those applications and synthesized to be tested *in vitro* and *in vivo*, as also described. Such ribozymes can also be optimized and delivered as described therein. While specific examples to mouse and human RNA are provided, those in the art will recognize that the equivalent human RNA targets described can be used as described below. Thus, the same target may be used, but binding arms suitable for targeting human RNA sequences are present in the ribozyme. Such targets may also be selected as described below.

The sequence of human and mouse *relA* mRNA can be screened for accessible sites using a computer folding algorithm. Potential hammerhead or hairpin ribozyme cleavage sites were identified. These sites are shown in Tables II, III, and VI - VII. (All sequences are 5' to 3' in the tables.) While mouse and human sequences can be screened and ribozymes thereafter designed, the human targetted sequences are of most utility. However, as discussed in Stinchcomb *et al. supra*, mouse targetted ribozmes are useful to test efficacy of action of the ribozyme prior to testing in humans. The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of ribozyme. (In Table II, lower case

letters indicate positions that are not conserved between the Human and the Mouse *rel* A sequences.)

Hammerhead ribozymes are designed that could bind and are individually analyzed by computer folding (Jaeger, J. A., et al., 1989, Proc. Natl. Acad. Sci. USA, **86**, 7706-7710) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Referring to Figure 6, mRNA is screened for accessible cleavage sites by the method described generally in Draper et al., WO/US93/04020 hereby incorporated by reference herein. Briefly, DNA oligonucleotides representing potential hammerhead ribozyme cleavage sites are synthesized. A polymerase chain reaction is used to generate a substrate for T7 RNA polymerase transcription from human or murine *rel* A cDNA clones. Labeled RNA transcripts are synthesized *in vitro* from the two templates. The oligonucleotides and the labeled transcripts are annealed, RNAseH is added and the mixtures are incubated for the designated times at 37°C. Reactions are stopped and RNA separated on sequencing polyacrylamide gels. The percentage of the substrate cleaved is determined by autoradiographic quantitation using a phosphor imaging system. From these data, hammerhead ribozyme sites are chosen as the most accessible.

Ribozymes of the hammerhead motif are designed to anneal to various sites in the mRNA message. The binding arms are complementary to the target site sequences described above. The ribozymes are chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman,N.; Ogilvie,K.K.; Jiang,M.-Y.; Cedergren,R.J. 1987, *J. Am. Chem. Soc.*, **109**, 7845-7854 and in Scaringe,S.A.; Franklyn,C.; Usman,N., 1990, *Nucleic Acids Res.*, **18**, 5433-5441 and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields were >98%. Inactive ribozymes were synthesized by substituting a U for G_5 and a U for A_{14} (numbering from (Hertel, K. J., et al., 1992, Nucleic

Acids Res., **20**, 3252)). Hairpin ribozymes are synthesized in two parts and annealed to reconstruct the active ribozyme (Chowrira, B. M. and Burke, J. M., 1992, Nucleic Acids Res., **20**, 2835-2840). All ribozymes are modified to enhance stability by modification of five ribonucleotides at both the 5' and 3' ends with 2'-*O*-methyl groups. Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Usman *et al.,* Synthesis, deprotection, analysis and purification of RNA and ribozymes, filed May, 18, 1994, U.S.S.N. 08/245,736 the totality of which is hereby incorporated herein by reference.) and are resuspended in water.

The sequences of the chemically synthesized ribozymes useful in this study are shown in Tables IV - VII. Those in the art will recognize that these sequences are representative only of many more such sequences where the enzymatic portion of the ribozyme (all but the binding arms) is altered to affect activity and may be formed of ribonucleotides or other nucleotides or non-nucleotides. Such ribozymes are equivalent to the ribozymes described specifically in the Tables.

Optimizing Ribozyme Activity

Ribozyme activity can be optimized as described by Stinchcomb *et al.*, supra. The details will not be repeated here, but include altering the length of the ribozyme binding arms (stems I and III, see Figure 2c), or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.,* Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, Nature 1990, *344*:565; Pieken *et al.*, Science 1991, *253*:314; Usman and Cedergren, *Trends in Biochem. Sci.* 1992, *17*:334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162, as well as Usman,N. *et al. US Patent Application 07/829,729,* and Sproat,B. *European Patent Application 92110298.4* which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules. All these publications are hereby incorporated by reference herein.), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan, *et al.*, supra, describes the general methods for delivery of enzymatic RNA molecules . Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intrvascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Sullivan, *et al.*, supra and Draper, *et al.*, supra which have been incorporated by reference herein.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein, O. and Moss, B., 1990, *Proc. Natl. Acad. Sci. U S A*, **87**, 6743-7; Gao, X. and Huang, L., 1993, *Nucleic Acids Res.*, **21**, 2867-72; Lieber, A., et al., 1993, *Methods Enzymol.*, **217**, 47-66; Zhou, Y., et al., 1990, *Mol. Cell. Biol.*, **10**, 4529-37). Several investigators have demonstrated that ribozymes expressed from such promoters can function in mammalian cells (e.g. (Kashani-Sabet, M., et al.,, 1992, *Antisense Res. Dev.*, **2**, 3-15; Ojwang, J. O., et al.,, 1992, *Proc. Natl. Acad. Sci. U S A*, **89**, 10802-6; Chen, C. J., et al.,, 1992, *Nucleic Acids Res.*, **20**, 4581-9; Yu, M., et al., 1993, *Proc. Natl. Acad. Sci. U S A*, **90**, 6340-4; L'Huillier, P. J., et al., 1992, *Embo J.*, **11**, 4411-8; Lisziewicz, J., et al., 1993, *Proc. Natl. Acad. Sci. U. S. A.*, **90**, 8000-4)). The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells,

including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral vectors).

In a preferred embodiment of the invention, a transcription unit expressing a ribozyme that cleaves *rel*A RNA is inserted into a plasmid DNA vector or an adenovirus DNA viral vector. Both vectors have been used to transfer genes to the intact vasculature or to joints of live animals (Willard, J. E., et al., 1992, Circulation, **86**, I-473.; Nabel, E. G., et al., 1990, Science, **249**, 1285-1288.) and both vectors lead to transient gene expression. The adenovirus vector is delivered as recombinant adenoviral particles. DNA may be delivered alone or complexed with vehicles (as described for RNA above). The DNA, DNA/vehicle complexes, or the recombinant adenovirus particles are locally administered to the site of treatment, *e.g.,* through the use of an injection catheter, stent or infusion pump or are directly added to cells or tissues *ex vivo*.

Example 1: NF–κB Hammerhead ribozymes

By engineering ribozyme motifs we have designed several ribozymes directed against *rel* A mRNA sequences. These ribozymes are synthesized with modifications that improve their nuclease resistance. The ability of ribozymes to cleave *rel*A target sequences *in vitro* is evaluated.

The ribozymes will be tested for function *in vivo* by analyzing cytokine-induced VCAM-1, ICAM-1, IL-6 and IL-8 expression levels. Ribozymes will be delivered to cells by incorporation into liposomes, by complexing with cationic lipids, by microinjection, or by expression from DNA vectors. Cytokine-induced VCAM-1, ICAM-1, IL-6 and IL-8 expression will be monitored by ELISA, by indirect immunofluoresence, and/or by FACS analysis. *Rel* A mRNA levels will be assessed by Northern analysis, RNAse protection or primer extension analysis or quantitative RT-PCR. Activity of NF–κB will be monitored by gel-retardation assays. Ribozymes that block the induction of NF–κB activity and/or *rel A* mRNA by more than 50% will be identified.

RNA ribozymes and/or genes encoding them will be locally delivered to transplant tissue *ex vivo* in animal models. Expression of the ribozyme will be monitored by its ability to block *ex vivo* induction of VCAM-1, ICAM-1, IL-6 and IL-8 mRNA and protein. The effect of the anti-*rel A* ribozymes

on graft rejection will then be assessed. Similarly, ribozymes will be introduced into joints of mice with collagen-induced arthritis or rabbits with *Streptococcal* cell wall-induced arthritis. Liposome delivery, cationic lipid delivery, or adeno-associated virus vector delivery can be used. One dose (or a few infrequent doses) of a stable anti-*relA* ribozyme or a gene construct that constitutively expresses the ribozyme may abrogate inflammatory and immune responses in these diseases.

Uses

A therapeutic agent that inhibits cytokine gene expression, inhibits adhesion molecule expression, and mimics the anti-inflammatory effects of glucocorticoids (without inducing steroid-responsive genes) is ideal for the treatment of inflammatory and autoimmune disorders. Disease targets for such a drug are numerous. Target indications and the delivery options each entails are summarized below. In all cases, because of the potential immunosuppressive properties of a ribozyme that cleaves *rel A* mRNA, uses are limited to local delivery, acute indications, or *ex vivo* treatment.

•Rheumatoid arthritis (RA).

Due to the chronic nature of RA, a gene therapy approach is logical. Delivery of a ribozyme to inflamed joints is mediated by adenovirus, retrovirus, or adeno-associated virus vectors. For instance, the appropriate adenovirus vector can be administered by direct injection into the synovium: high efficiency of gene transfer and expression for several months would be expected (B.J. Roessler, E.D. Allen, J.M. Wilson, J.W. Hartman, B. L. Davidson, J. Clin. Invest. 92, 1085-1092 (1993)). It is unlikely that the course of the disease could be reversed by the transient, local administration of an anti-inflammatory agent. Multiple administrations may be necessary. Retrovirus and adeno-associated virus vectors would lead to permanent gene transfer and expression in the joint. However, permanent expression of a potent anti-inflammatory agent may lead to local immune deficiency.

•Restenosis.

Expression of NF–κB in the vessel wall of pigs causes a narrowing of the luminal space due to excessive deposition of extracellular matrix components. This phenotype is similar to matrix deposition that occurs

subsequent to coronary angioplasty. In addition, NF–κB is required for the expression of the oncogene c-myb (F.A. La Rosa, J.W. Pierce, G.E. Soneneshein, Mol. Cell. Biol. 14, 1039-44 (1994)). Thus NF–κB induces smooth muscle proliferation and the expression of excess matrix components: both processes are thought to contribute to reocclusion of vessels after coronary angioplasty.

•Transplantation.

NF–κB is required for the induction of adhesion molecules (Eck et al., *supra*, K. O'Brien, et al., J. Clin. Invest. 92, 945-951 (1993)) that function in immune recognition and inflammatory responses. At least two potential modes of treatment are possible. In the first, transplanted organs are treated *ex vivo* with ribozymes or ribozyme expression vectors. Transient inhibition of NF–κB in the transplanted endothelium may be sufficient to prevent transplant-associated vasculitis and may significantly modulate graft rejection. In the second, donor B cells are treated *ex vivo* with ribozymes or ribozyme expression vectors. Recipients would receive the treatment prior to transplant. Treatment of a recipient with B cells that do not express T cell co-stimulatory molecules (such as ICAM-1, VCAM-1, and/or B7 an B7-2) can induce antigen-specific anergy. Tolerance to the donor's histocompatibility antigens could result; potentially, any donor could be used for any transplantation procedure.

•Asthma.

Granulocyte macrophage colony stimulating factor (GM-CSF) is thought to play a major role in recruitment of eosinophils and other inflammatory cells during the late phase reaction to asthmatic trauma. Again, blocking the local induction of GM-CSF and other inflammatory mediators is likely to reduce the persistent inflammation observed in chronic asthmatics. Aerosol delivery of ribozymes or adenovirus ribozyme expression vectors is a feasible treatment.

•Gene Therapy.

Immune responses limit the efficacy of many gene transfer techniques. Cells transfected with retrovirus vectors have short lifetimes in immune competent individuals. The length of expression of adenovirus vectors in terminally differentiated cells is longer in neonatal or immune-

compromised animals. Insertion of a small ribozyme expression cassette that modulates inflammatory and immune responses into existing adenovirus or retrovirus constructs will greatly enhance their potential.

Thus, ribozymes of the present invention that cleave *rel A* mRNA and thereby NF–κB activity have many potential therapeutic uses, and there are reasonable modes of delivering the ribozymes in a number of the possible indications. Development of an effective ribozyme that inhibits NF–κB function is described above; available cellular and activity assays are number, reproducible, and accurate. Animal models for NF–κB function (Kitajima, et al., *supra*) and for each of the suggested disease targets exist and can be used to optimize activity.

Diagnostic uses

Ribozymes of this invention may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes described in this invention, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other in vitro uses of ribozymes of this invention are well known in the art, and include detection of the presence of mRNA associated with an NF–κB related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

In a specific example, ribozymes which can cleave only wild-type or mutant forms of the target RNA are used for the assay. The first ribozyme is

used to identify wild-type RNA present in the sample and the second ribozyme will be used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA will be cleaved by both ribozymes to demonstrate the relative ribozyme efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates will also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis will require two ribozymes, two substrates and one unknown sample which will be combined into six reactions. The presence of cleavage products will be determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, NF-κB) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios will be correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

Other embodiments are within the following claims.

TABLE I

Characteristics of Ribozymes

Group I Introns
Size: ~**200** to >1000 nucleotides.
Requires a U in the target sequence immediately 5' of the cleavage site.
Binds 4-6 nucleotides at 5' side of cleavage site.
Over 75 known members of this class. Found in *Tetrahymena thermophila* rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.

RNAseP RNA (M1 RNA)
Size: ~290 to 400 nucleotides.
RNA portion of a ribonucleoprotein enzyme. Cleaves tRNA precursors to form mature tRNA.
Roughly 10 known members of this group all are bacterial in origin.

Hammerhead Ribozyme
Size: ~**13** to 40 nucleotides.
Requires the target sequence UH immediately 5' of the cleavage site.
Binds a variable number nucleotides on both sides of the cleavage site.
14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent (Figures 1 and 2 show examples of various manifestations as used in the art).

Hairpin Ribozyme
Size: ~50 nucleotides.
Requires the target sequence GUC immediately 3' of the cleavage site.
Binds **4-6** nucleotides at 5' side of the cleavage site and a variable number to the 3' side of the cleavage site.
Only **3** known member of this class. Found in **three** plant pathogen (satellite RNAs of the tobacco ringspot virus, **arabis mosaic virus and chicory yellow mottle virus**) which uses RNA as the infectious agent (Figure 3).

Hepatitis Delta Virus (HDV) Ribozyme
Size: **50 - 60** nucleotides (at present).
Cleavage of target RNAs recently demonstrated.
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required.
Only 1 known member of this class. Found in human HDV (Figure 4).

***Neurospora* VS RNA Ribozyme**

Size: ~144 nucleotides (at present)

Cleavage of target RNAs recently demonstrated.
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined. Only 1 known member of this class. Found in *Neurospora* VS RNA (Figure 5).

Table II

Mouse *rel A* HH Target sequence

nt. Pos.	HH Target Sequence	Seq. ID No.	nt. Pos.	HH Target Sequence	Seq. ID No.
19	AAUGGCU a caCaGgA	7	467	cCAGGCU c cuguUCg	108
22	aGCUCcU a cGUgGUG	8	469	AaGCcAU u AGcCAGC	109
26	CcUCcaU u GcGgACa	9	473	UuUgAGU C AGauCAg	110
93	GAuCUGU U uCCCCUC	10	481	AGCGaAU C CAGACCA	111
94	AuCUGUU u CCCCUCA	11	501	AACCCCU U uCAcGUU	112
100	UuCCCCU C AUCUUuC	12	502	ACCCCUU u CAcGUUC	113
103	CCCUCAU C UuuCCcu	13	508	UuCAcGU U CCUAUAG	114
105	CUCAUCU U uCCcuCA	14	509	uCAcGUU C CUAUAGA	115
106	UCAUCUU u CccuCAG	15	512	cGUUCCU A UAGAgGA	116
129	CAGGCuU C UGGgCCu	16	514	UUCCUAU A GAgGAGC	117
138	GGgCCuU A UGUGGAG	17	534	GGGGACU A uGACuUG	118
148	UGGAGAU C AucGAaC	18	556	UGCGcCU C UGCUUCC	119
151	AGAUCAU c GaaCAGC	19	561	CUCUGCU U CCAGGUG	120
180	AUGCGaU U CCGCUAu	20	562	UCUGCUU C CAGGUGA	121
181	UGCGaUU C CGCUAuA	21	585	aAgCCAU u AGcCAGc	122
186	UUCCGCU A uAAaUGC	22	598	GGCCCCU C CuCCUGa	123
204	GGGCGCU C aGCGGGC	23	613	CcCCUGU C CUcuCaC	124
217	GCAGuAU u CcuGGCG	24	616	CUGUCCU c uCaCAUC	125
239	CACAGAU A CCACCAA	25	617	gucCCUU C CUCAgCC	126
262	CCACCAU C AAGAUCA	26	620	CCUUCCU C AgCCaug	127
268	UCAAGAU C AAUGGCU	27	623	UCCUgcU u CCAUCUc	128
276	AAUGGCU A CACAGGA	28	628	AUCCgAU u UUUGAuA	129
301	UuCGaAU C UCCCUGG	29	630	CCgAUuU U UGAuAAc	130
303	CGaAUCU C CCUGGUC	30	631	CgAUuUU U GAuAAcC	131
310	CCCUGGU C ACCAAGG	31	638	UGgCcAU u GUGuuCC	132
323	GGcCCCU C CUCcuga	32	661	CCGAGCU C AAGAUCU	133
326	uCCaCCU C ACCGGCC	33	667	UCAAGAU C UGCCGAG	134
335	CCGGCCU C AuCCaCA	34	687	CGgAACU C UGGgAGC	135
349	AuGAaCU U GugGGgA	35	700	GCUGCCU C GGUGGGG	136
352	AGaUcaU c GaAcAGc	36	715	AUGAGAU C UUCuUgC	137
375	GAUGGCU a CUAUGAG	37	717	GAGAUCU U CuUgCUG	138
376	AUGGucU C UccGgaG	38	718	AGAUCUU C uUgCUGU	139
378	GGCUaCU A UGAGGCU	39	721	UucUCCU c CauUGcG	140
391	CUGAcCU C UGCCCaG	40	751	AaGACAU U GAGGUGU	141
409	GCaGuAU C CauAGcU	41	759	GAGGUGU A UUUCACG	142
416	CCgCAGU a UCCAuAg	42	761	GGUGUAU U UCACGGG	143
417	CAuAGcU U CCAGAAC	43	762	GUGUAUU U CACGGGA	144
418	AuAGcUU C CAGAACC	44	763	UGUAUUU C ACGGGAC	145
433	UGGGgAU C CAGUGUG	45	792	CGAGGCU C CUUUUCu	146
795	GGCUCCU U UUCuCAA	46	1167	GAUGAGU U UuCCcCC	147
796	GCUCCUU U UcuCAAG	47	1168	AUGAGUU U uCCcCCA	148
797	CUCCUUU U CuCAAGC	48	1169	UGAGUUU u CCcCCAU	149
798	UCCUUUU C uCAAGCU	49	1182	AUGcUGU U aCCaUCa	150
829	UGGCCAU U GUGUUCC	50	1183	UGcUGUU a CCaUCaG	151
834	AUUGUGU U CCGGACu	51	1184	GGccccU C CUcCUGa	152
835	UUGUGUU C CGGACuC	52	1187	GUccCuU c CUcaGCc	153
845	GACuCCU C CgUACGC	53	1188	UUaCCaU C aGGGCAG	154
849	CCUCCgU A CGCcGAC	54	1198	GGgAGuU u AGuCuGa	155

872	cCAGGCU C CUGUuCG	55	1209	CAGcCCU a caCCUUc	156
883	UuCGaGU C UCCAUGC	56	1215	cuGGCCU U aGCaCCG	157
885	CGaGUCU C CAUGCAG	57	1229	GGuCCCU u CCucAGc	158
905	GCGGCCU U CuGAuCG	58	1237	CCCAgcU C CUGCCCC	159
906	CGGCCUU C uGAuCGc	59	1250	CCAGcCU C CAGgCuC	160
919	GcGAGCU C AGUGAGC	60	1268	CCCaGCU C CuGCCcc	161
936	AUGGAgU U CCAGUAC	61	1279	CCAUGGU c cCuuCcu	162
937	UGGAgUU C CAGUACu	62	1281	gUGGgcU C AGCUgcG	163
942	UUCCAGU A CuUGCCA	63	1286	AUgAGuU u UccCCCA	164
953	GCCucAU c CacAuGA	64	1309	CuCCUGU u CgAGUCu	165
962	AGAuGAU C GcCACCG	65	1315	cCCCAGU u CUAaCCC	166
965	CagUacU u gCCaGAc	66	1318	CAGUuCU A aCCCCgG	167
973	ACCGGAU U GaaGAGA	67	1331	gGGuCCU C CcCAGuC	168
986	GAgACcU u cAAGagu	68	1334	CuuUuCU C AaGCUGa	169
996	AGGACcU A UGAGACC	69	1389	ACGCUGU C gGAaGCC	170
1005	GAGACCU U CAAGAGu	70	1413	CUGCAGU U UGAUGcU	171
1006	AGACCUU C AAGAGuA	71	1414	UGCAGUU U GAUGcUG	172
1015	AGAGuAU C AUGAAGA	72	1437	GGGGCCU U GCUUGGC	173
1028	GAAGAGU C CUUUCAa	73	1441	CCUUGCU U GGCAACA	174
1031	GAGUCCU U UCAauGG	74	1467	GgaGUGU U CACAGAC	175
1032	AGUCCUU U CaauGGA	75	1468	gaGUGUU C ACAGACC	176
1033	GUCCUUU C AauGGAC	76	1482	CUGGCAU C uGUgGAC	177
1058	CCGGCCU C CaaCcCG	77	1486	CuUCgGU a GggAACU	178
1064	UaCACCU u GaucCAa	78	1494	GACAACU C aGAGUUU	179
1072	GgCGuAU U GCUGUGC	79	1500	UCaGAGU U UCAGCAG	180
1082	UGUGCCU a CCCGaAa	80	1501	CaGAGUU U CAGCAGC	181
1083	aaGCCUU C CCGaAGu	81	1502	aGAGUUU C AGCAGCU	182
1092	CGaAaCU C AaCUUCU	82	1525	gGuGCAU c CCUGUGu	183
1097	CUCAaCU U CUGUCCC	83	1566	AUGGAGU A CCCUGAa	184
1098	UCAaCUU C UGUCCCC	84	1577	UGAaGCU A UAACUCG	185
1102	CUUCUGU C CCCAAGC	85	1579	AaGCUAU A ACUCGCC	186
1125	CAGCCCU A caCCUUc	86	1583	UAUAACU C GCCUgGU	187
1127	GCCaUAU a gCcUUAC	87	1588	CUCuCCU A GaGAggG	188
1131	cAUCCCU c agCacCA	88	1622	CCCAGCU C CUGCcCC	189
1132	AcaCCUU c cCagCAU	89	1628	UCCUGCU u CggUaGG	190
1133	UCCaUcU c CagCuUC	90	1648	CGGGGCU u CCCAAUG	191
1137	UUUACuU u AgCgCgc	91	1660	cUGaCCU C ugccCAG	192
1140	cCagCAU C CCUcAGC	92	1663	cuCUgCU U cCAGGuG	193
1153	GCACCAU C AACUuUG	93	1664	uCUgCUU c CAGGuGA	194
1158	AUCAACU u UGAUGAG	94	1665	CUCgcUU u cGGAGgU	195
1680	GAAGACU U CUCCUCC	95			
1681	AAGACUU C UCCUCCA	96			
1683	GACUUCU C CUCCAUU	97			
1686	UUCUCCU C CAUUGCG	98			
1690	CCUCCAU U GCGGACA	99			
1704	AUGGACU U CUCuGCu	100			
1705	UGGACUU C UCuGCuC	101			
1707	GACUUCU C uGCuCUu	102			
1721	uuUGAGU C AGAUCAG	103			
1726	GUCAGAU C AGCUCCU	104			
1731	AUCAGCU C CUAAGGu	105			
1734	AGCUCCU A AGGuGcU	106			
1754	CaGugCU C CCaAGAG	107			

Table III

Human *rel A* HH Target Sequences

nt. Pos.	HH Target Sequence	Seq. ID No.	nt. Pos.	HH Target Sequence	Seq. ID No.
19	AAUGGCU C GUCUGUA	196	467	GCAGGCU A UCAGUCA	297
22	GGCUCGU C UGUAGUG	197	469	AGGCUAU C AGUCAGC	298
26	CGUCUGU A GUGCACG	198	473	UAUCAGU C AGCGCAU	299
93	GAACUGU U CCCCCUC	199	481	AGCGCAU C CAGACCA	300
94	AACUGUU C CCCCUCA	200	501	AACCCCU U CCAAGUU	301
100	UCCCCCU C AUCUUCC	201	502	ACCCCUU C CAAGUUC	302
103	CCCUCAU C UUCCCGG	202	508	UCCAAGU U CCUAUAG	303
105	CUCAUCU U CCCGGCA	203	509	CCAAGUU C CUAUAGA	304
106	UCAUCUU C CCGGCAG	204	512	AGUUCCU A UAGAAGA	305
129	CAGGCCU C UGGCCCC	205	514	UUCCUAU A GAAGAGC	306
138	GGCCCCU A UGUGGAG	206	534	GGGGACU A CGACCUG	307
148	UGGAGAU C AUUGAGC	207	556	UGCGGCU C UGCUUCC	308
151	AGAUCAU U GAGCAGC	208	561	CUCUGCU U CCAGGUG	309
180	AUGCGCU U CCGCUAC	209	562	UCUGCUU C CAGGUGA	310
181	UGCGCUU C CGCUACA	210	585	GACCCAU C AGGCAGG	311
186	UUCCGCU A CAAGUGC	211	598	GGCCCCU C CGCCUGC	312
204	GGGCGCU C CGCGGGC	212	613	CGCCUGU C CUUCCUC	313
217	GCAGCAU C CCAGGCG	213	616	CUGUCCU U CCUCAUC	314
239	CACAGAU A CCACCAA	214	617	UGUCCUU C CUCAUCC	315
262	CCACCAU C AAGAUCA	215	620	CCUUCCU C AUCCCAU	316
268	UCAAGAU C AAUGGCU	216	623	UCCUCAU C CCAUCUU	317
276	AAUGGCU A CACAGGA	217	628	AUCCCAU C UUUGACA	318
301	UGCGCAU C UCCCUGG	218	630	CCCAUCU U UGACAAU	319
303	CGCAUCU C CCUGGUC	219	631	CCAUCUU U GACAAUC	320
310	CCCUGGU C ACCAAGG	220	638	UGACAAU C GUGCCCC	321
323	GGACCCU C CUCACCG	221	661	CCGAGCU C AAGAUCU	322
326	CCCUCCU C ACCGGCC	222	667	UCAAGAU C UGCCGAG	323
335	CCGGCCU C ACCCCCA	223	687	CGAAACU C UGGCAGC	324
349	ACGAGCU U GUAGGAA	224	700	GCUGCCU C GGUGGGG	325
352	AGCUUGU A GGAAAGG	225	715	AUGAGAU C UUCCUAC	326
375	GAUGGCU U CUAUGAG	226	717	GAGAUCU U CCUACUG	327
376	AUGGCUU C UAUGAGG	227	718	AGAUCUU C CUACUGU	328
378	GGCUUCU A UGAGGCU	228	721	UCUUCCU A CUGUGUG	329
391	CUGAGCU C UGCCCGG	229	751	AGGACAU U GAGGUGU	330
409	GCUGCAU C CACAGUU	230	759	GAGGUGU A UUUCACG	331
416	CCACAGU U UCCAGAA	231	761	GGUGUAU U UCACGGG	332
417	CACAGUU U CCAGAAC	232	762	GUGUAUU U CACGGGA	333
418	ACAGUUU C CAGAACC	233	763	UGUAUUU C ACGGGAC	334
433	UGGGAAU C CAGUGUG	234	792	CGAGGCU C CUUUUCG	335
795	GGCUCCU U UUCGCAA	235	1167	GAUGAGU U UCCCACC	336
796	GCUCCUU U UCGCAAG	236	1168	AUGAGUU U CCCACCA	337
797	CUCCUUU U CGCAAGC	237	1169	UGAGUUU C CCACCAU	338
798	UCCUUUU C GCAAGCU	238	1182	AUGGUGU U UCCUUCU	339
829	UGGCCAU U GUGUUCC	239	1183	UGGUGUU U CCUUCUG	340
834	AUUGUGU U CCGGACC	240	1184	GGUGUUU C CUUCUGG	341
835	UUGUGUU C CGGACCC	241	1187	GUUUCCU U CUGGGCA	342
845	GACCCCU C CCUACGC	242	1188	UUUCCUU C UGGGCAG	343
849	CCUCCCU A CGCAGAC	243	1198	GGCAGAU C AGCCAGG	344
872	GCAGGCU C CUGUGCG	244	1209	CAGGCCU C GGCCUUG	345
883	UGCGUGU C UCCAUGC	245	1215	UCGGCCU U GGCCCCG	346

885	CGUGUCU C CAUGCAG	246	1229	GGCCCCU C CCCAAGU	347
905	GCGGCCU U CCGACCG	247	1237	CCCAAGU C CUGCCCC	348
906	CGGCCUU C CGACCGG	248	1250	CCAGGCU C CAGCCCC	349
919	GGGAGCU C AGUGAGC	249	1268	CCCUGCU C CAGCCAU	350
936	AUGGAAU U CCAGUAC	250	1279	CCAUGGU A UCAGCUC	351
937	UGGAAUU C CAGUACC	251	1281	AUGGUAU C AGCUCUG	352
942	UUCCAGU A CCUGCCA	252	1286	AUCAGCU C UGGCCCA	353
953	GCCAGAU A CAGACGA	253	1309	CCCCUGU C CCAGUCC	354
962	AGACGAU C GUCACCG	254	1315	UCCCAGU C CUAGCCC	355
965	CGAUCGU C ACCGGAU	255	1318	CAGUCCU A GCCCCAG	356
973	ACCGGAU U GAGGAGA	256	1331	AGGCCCU C CUCAGGC	357
986	GAAACGU A AAAGGAC	257	1334	CCCUCCU C AGGCUGU	358
996	AGGACAU A UGAGACC	258	1389	ACGCUGU C AGAGGCC	359
1005	GAGACCU U CAAGAGC	259	1413	CUGCAGU U UGAUGAU	360
1006	AGACCUU C AAGAGCA	260	1414	UGCAGUU U GAUGAUG	361
1015	AGAGCAU C AUGAAGA	261	1437	GGGGCCU U GCUUGGC	362
1028	GAAGAGU C CUUUCAG	262	1441	CCUUGCU U GGCAACA	363
1031	GAGUCCU U UCAGCGG	263	1467	GCUGUGU U CACAGAC	364
1032	AGUCCUU U CAGCGGA	264	1468	CUGUGUU C ACAGACC	365
1033	GUCCUUU C AGCGGAC	265	1482	CUGGCAU C CGUCGAC	366
1058	CCGGCCU C CACCUCG	266	1486	CAUCCGU C GACAACU	367
1064	UCCACCU C GACGCAU	267	1494	GACAACU C CGAGUUU	368
1072	GACGCAU U GCUGUGC	268	1500	UCCGAGU U UCAGCAG	369
1082	UGUGCCU U CCCGCAG	269	1501	CCGAGUU U CAGCAGC	370
1083	GUGCCUU C CCGCAGC	270	1502	CGAGUUU C AGCAGCU	371
1092	CGCAGCU C AGCUUCU	271	1525	AGGGCAU A CCUGUGG	372
1097	CUCAGCU U CUGUCCC	272	1566	AUGGAGU A CCCUGAG	373
1098	UCAGCUU C UGUCCCC	273	1577	UGAGGCU A UAACUCG	374
1102	CUUCUGU C CCCAAGC	274	1579	AGGCUAU A ACUCGCC	375
1125	CAGCCCU A UCCCUUU	275	1583	UAUAACU C GCCUAGU	376
1127	GCCCUAU C CCUUUAC	276	1588	CUCGCCU A GUGACAG	377
1131	UAUCCCU U UACGUCA	277	1622	CCCAGCU C CUGCUCC	378
1132	AUCCCUU U ACGUCAU	278	1628	UCCUGCU C CACUGGG	379
1133	UCCCUUU A CGUCAUC	279	1648	CGGGGCU C CCCAAUG	380
1137	UUUACGU C AUCCCUG	280	1660	AUGGCCU C CUUUCAG	381
1140	ACGUCAU C CCUGAGC	281	1663	GCCUCCU U UCAGGAG	382
1153	GCACCAU C AACUAUG	282	1664	CCUCCUU U CAGGAGA	383
1158	AUCAACU A UGAUGAG	283	1665	CUCCUUU C AGGAGAU	384
1680	GAAGACU U CUCCUCC	284			
1681	AAGACUU C UCCUCCA	285			
1683	GACUUCU C CUCCAUU	286			
1686	UUCUCCU C CAUUGCG	287			
1690	CCUCCAU U GCGGACA	288			
1704	AUGGACU U CUCAGCC	289			
1705	UGGACUU C UCAGCCC	290			
1707	GACUUCU C AGCCCUG	291			
1721	GCUGAGU C AGAUCAG	292			
1726	GUCAGAU C AGCUCCU	293			
1731	AUCAGCU C CUAAGGG	294			
1734	AGCUCCU A AGGGGGU	295			
1754	CUGCCCU C CCCAGAG	296			

Table IV

Mouse *rel A* HH Ribozyme Sequences

nt. Seq.	HH Ribozyme Sequence	Seq. ID No.
19	UCCUGUG CUGAUGAGGCCGAAAGGCCGAA AGCCAUU	385
22	CACCACG CUGAUGAGGCCGAAAGGCCGAA AGGAGCU	386
26	UGUCCGC CUGAUGAGGCCGAAAGGCCGAA AUGGAGG	387
93	GAGGGGA CUGAUGAGGCCGAAAGGCCGAA ACAGAUC	388
94	UGAGGGG CUGAUGAGGCCGAAAGGCCGAA AACAGAU	389
100	GAAAGAU CUGAUGAGGCCGAAAGGCCGAA AGGGGAA	390
103	AGGGAAA CUGAUGAGGCCGAAAGGCCGAA AUGAGGG	391
105	UGAGGGA CUGAUGAGGCCGAAAGGCCGAA AGAUGAG	392
106	CUGAGGG CUGAUGAGGCCGAAAGGCCGAA AAGAUGA	393
129	AGGCCCA CUGAUGAGGCCGAAAGGCCGAA AAGCCUG	394
138	CUCCACA CUGAUGAGGCCGAAAGGCCGAA AAGGCCC	395
148	GUUCGAU CUGAUGAGGCCGAAAGGCCGAA AUCUCCA	396
151	GCUGUUC CUGAUGAGGCCGAAAGGCCGAA AUGAUCU	397
180	AUAGCGG CUGAUGAGGCCGAAAGGCCGAA AUCGCAU	398
181	UAUAGCG CUGAUGAGGCCGAAAGGCCGAA AAUCGCA	399
186	GCAUUUA CUGAUGAGGCCGAAAGGCCGAA AGCGGAA	400
204	GCCCGCU CUGAUGAGGCCGAAAGGCCGAA AGCGCCC	401
217	CGCCAGG CUGAUGAGGCCGAAAGGCCGAA AUACUGC	402
239	UUGGUGG CUGAUGAGGCCGAAAGGCCGAA AUCUGUG	403
262	UGAUCUU CUGAUGAGGCCGAAAGGCCGAA AUGGUGG	404
268	AGCCAUU CUGAUGAGGCCGAAAGGCCGAA AUCUUGA	405
276	UCCUGUG CUGAUGAGGCCGAAAGGCCGAA AGCCAUU	406
301	CCAGGGA CUGAUGAGGCCGAAAGGCCGAA AUUCGAA	407
303	GACCAGG CUGAUGAGGCCGAAAGGCCGAA AGAUUCG	408
310	CCUUGGU CUGAUGAGGCCGAAAGGCCGAA ACCAGGG	409
323	UCAGGAG CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	410
326	GGCCGGU CUGAUGAGGCCGAAAGGCCGAA AGGUGGA	411
335	UGUGGAU CUGAUGAGGCCGAAAGGCCGAA AGGCCGG	412
349	UCCCCAC CUGAUGAGGCCGAAAGGCCGAA AGUUCAU	413
352	GCUGUUC CUGAUGAGGCCGAAAGGCCGAA AUGAUCU	414
375	CUCAUAG CUGAUGAGGCCGAAAGGCCGAA AGCCAUC	415
376	CUCCGGA CUGAUGAGGCCGAAAGGCCGAA AGACCAU	416
378	AGCCUCA CUGAUGAGGCCGAAAGGCCGAA AGUAGCC	417
391	CUGGGCA CUGAUGAGGCCGAAAGGCCGAA AGGUCAG	418
409	AGCUAUG CUGAUGAGGCCGAAAGGCCGAA AUACUGC	419
416	CUAUGGA CUGAUGAGGCCGAAAGGCCGAA ACUGCGG	420
417	GUUCUGG CUGAUGAGGCCGAAAGGCCGAA AGCUAUG	421
418	GGUUCUG CUGAUGAGGCCGAAAGGCCGAA AAGCUAU	422
433	CACACUG CUGAUGAGGCCGAAAGGCCGAA AUCCCCA	423
467	CGAACAG CUGAUGAGGCCGAAAGGCCGAA AGCCUGG	424
469	GCUGGCU CUGAUGAGGCCGAAAGGCCGAA AUGGCUU	425
473	CUGAUCU CUGAUGAGGCCGAAAGGCCGAA ACUCAAA	426
481	UGGUCUG CUGAUGAGGCCGAAAGGCCGAA AUUCGCU	427
501	AACGUGA CUGAUGAGGCCGAAAGGCCGAA AGGGGUU	428
502	GAACGUG CUGAUGAGGCCGAAAGGCCGAA AAGGGGU	429
508	CUAUAGG CUGAUGAGGCCGAAAGGCCGAA ACGUGAA	430
509	UCUAUAG CUGAUGAGGCCGAAAGGCCGAA AACGUGA	431
512	UCCUCUA CUGAUGAGGCCGAAAGGCCGAA AGGAACG	432
514	GCUCCUC CUGAUGAGGCCGAAAGGCCGAA AUAGGAA	433
534	CAAGUCA CUGAUGAGGCCGAAAGGCCGAA AGUCCCC	434

556	GGAAGCA CUGAUGAGGCCGAAAGGCCGAA AGGCGCA	435
561	CACCUGG CUGAUGAGGCCGAAAGGCCGAA AGCAGAG	436
562	UCACCUG CUGAUGAGGCCGAAAGGCCGAA AAGCAGA	437
585	GCUGGCU CUGAUGAGGCCGAAAGGCCGAA AUGGCUU	438
598	UCAGGAG CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	439
613	GUGAGAG CUGAUGAGGCCGAAAGGCCGAA ACAGGGG	440
616	GAUGUGA CUGAUGAGGCCGAAAGGCCGAA AGGACAG	441
617	GGCUGAG CUGAUGAGGCCGAAAGGCCGAA AAGGGAC	442
620	CAUGGCU CUGAUGAGGCCGAAAGGCCGAA AGGAAGG	443
623	GAGAUGG CUGAUGAGGCCGAAAGGCCGAA AGCAGGA	444
628	UAUCAAA CUGAUGAGGCCGAAAGGCCGAA AUCGGAU	445
630	GUUAUCA CUGAUGAGGCCGAAAGGCCGAA AAAUCGG	446
631	GGUUAUC CUGAUGAGGCCGAAAGGCCGAA AAAAUCG	447
638	GGAACAC CUGAUGAGGCCGAAAGGCCGAA AUGGCCA	448
661	AGAUCUU CUGAUGAGGCCGAAAGGCCGAA AGCUCGG	449
667	CUCGGCA CUGAUGAGGCCGAAAGGCCGAA AUCUUGA	450
687	GCUCCCA CUGAUGAGGCCGAAAGGCCGAA AGUUCCG	451
700	CCCCACC CUGAUGAGGCCGAAAGGCCGAA AGGCAGC	452
715	GCAAGAA CUGAUGAGGCCGAAAGGCCGAA AUCUCAU	453
717	CAGCAAG CUGAUGAGGCCGAAAGGCCGAA AGAUCUC	454
718	ACAGCAA CUGAUGAGGCCGAAAGGCCGAA AAGAUCU	455
721	CGCAAUG CUGAUGAGGCCGAAAGGCCGAA AGGAGAA	456
751	ACACCUC CUGAUGAGGCCGAAAGGCCGAA AUGUCUU	457
759	CGUGAAA CUGAUGAGGCCGAAAGGCCGAA ACACCUC	458
761	CCCGUGA CUGAUGAGGCCGAAAGGCCGAA AUACACC	459
762	UCCCGUG CUGAUGAGGCCGAAAGGCCGAA AAUACAC	460
763	GUCCCGU CUGAUGAGGCCGAAAGGCCGAA AAAUACA	461
792	AGAAAAG CUGAUGAGGCCGAAAGGCCGAA AGCCUCG	462
795	UUGAGAA CUGAUGAGGCCGAAAGGCCGAA AGGAGCC	463
796	CUUGAGA CUGAUGAGGCCGAAAGGCCGAA AAGGAGC	464
797	GCUUGAG CUGAUGAGGCCGAAAGGCCGAA AAAGGAG	465
798	AGCUUGA CUGAUGAGGCCGAAAGGCCGAA AAAAGGA	466
829	GGAACAC CUGAUGAGGCCGAAAGGCCGAA AUGGCCA	467
834	AGUCCGG CUGAUGAGGCCGAAAGGCCGAA ACACAAU	468
835	GAGUCCG CUGAUGAGGCCGAAAGGCCGAA AACACAA	469
845	GCGUACG CUGAUGAGGCCGAAAGGCCGAA AGGAGUC	470
849	GUCGGCG CUGAUGAGGCCGAAAGGCCGAA ACGGAGG	471
872	CGAACAG CUGAUGAGGCCGAAAGGCCGAA AGCCUGG	472
883	GCAUGGA CUGAUGAGGCCGAAAGGCCGAA ACUCGAA	473
885	CUGCAUG CUGAUGAGGCCGAAAGGCCGAA AGACUCG	474
905	CGAUCAG CUGAUGAGGCCGAAAGGCCGAA AGGCCGC	475
906	GCGAUCA CUGAUGAGGCCGAAAGGCCGAA AAGGCCG	476
919	GCUCACU CUGAUGAGGCCGAAAGGCCGAA AGCUCGC	477
936	GUACUGG CUGAUGAGGCCGAAAGGCCGAA ACUCCAU	478
937	AGUACUG CUGAUGAGGCCGAAAGGCCGAA AACUCCA	479
942	UGGCAAG CUGAUGAGGCCGAAAGGCCGAA ACUGGAA	480
953	UCAUGUG CUGAUGAGGCCGAAAGGCCGAA AUGAGGC	481
962	CGGUGGC CUGAUGAGGCCGAAAGGCCGAA AUCAUCU	482
965	GUCUGGC CUGAUGAGGCCGAAAGGCCGAA AGUACUG	483
973	UCUCUUC CUGAUGAGGCCGAAAGGCCGAA AUCCGGU	484
986	ACUCUUG CUGAUGAGGCCGAAAGGCCGAA AGGUCUC	485
996	GGUCUCA CUGAUGAGGCCGAAAGGCCGAA AGGUCCU	486
1005	ACUCUUG CUGAUGAGGCCGAAAGGCCGAA AGGUCUC	487
1006	UACUCUU CUGAUGAGGCCGAAAGGCCGAA AAGGUCU	488
1015	UCUUCAU CUGAUGAGGCCGAAAGGCCGAA AUACUCU	489
1028	UUGAAAG CUGAUGAGGCCGAAAGGCCGAA ACUCUUC	490
1031	CCAUUGA CUGAUGAGGCCGAAAGGCCGAA AGGACUC	491

1032	UCCAUUG CUGAUGAGGCCGAAAGGCCGAA AAGGACU	492
1033	GUCCAUU CUGAUGAGGCCGAAAGGCCGAA AAAGGAC	493
1058	CGGGUUG CUGAUGAGGCCGAAAGGCCGAA AGGCCGG	494
1064	UUGGAUC CUGAUGAGGCCGAAAGGCCGAA AGGUGUA	495
1072	GCACAGC CUGAUGAGGCCGAAAGGCCGAA AUACGCC	496
1082	UUUCGGG CUGAUGAGGCCGAAAGGCCGAA AGGCACA	497
1083	ACUUCGG CUGAUGAGGCCGAAAGGCCGAA AAGGCUU	498
1092	AGAAGUU CUGAUGAGGCCGAAAGGCCGAA AGUUUCG	499
1097	GGGACAG CUGAUGAGGCCGAAAGGCCGAA AGUUGAG	500
1098	GGGGACA CUGAUGAGGCCGAAAGGCCGAA AAGUUGA	501
1102	GCUUGGG CUGAUGAGGCCGAAAGGCCGAA ACAGAAG	502
1125	GAAGGUG CUGAUGAGGCCGAAAGGCCGAA AGGGCUG	503
1127	GUAAGGC CUGAUGAGGCCGAAAGGCCGAA AUAUGGC	504
1131	UGGUGCU CUGAUGAGGCCGAAAGGCCGAA AGGGAUG	505
1132	AUGCUGG CUGAUGAGGCCGAAAGGCCGAA AAGGUGU	506
1133	GAAGCUG CUGAUGAGGCCGAAAGGCCGAA AGAUGGA	507
1137	GCGCGCU CUGAUGAGGCCGAAAGGCCGAA AAGUAAA	508
1140	GCUGAGG CUGAUGAGGCCGAAAGGCCGAA AUGCUGG	509
1153	CAAAGUU CUGAUGAGGCCGAAAGGCCGAA AUGGUGC	510
1158	CUCAUCA CUGAUGAGGCCGAAAGGCCGAA AGUUGAU	511
1167	GGGGGAA CUGAUGAGGCCGAAAGGCCGAA ACUCAUC	512
1168	UGGGGGA CUGAUGAGGCCGAAAGGCCGAA AACUCAU	513
1169	AUGGGGG CUGAUGAGGCCGAAAGGCCGAA AAACUCA	514
1182	UGAUGGU CUGAUGAGGCCGAAAGGCCGAA ACAGCAU	515
1183	CUGAUGG CUGAUGAGGCCGAAAGGCCGAA AACAGCA	516
1184	UCAGGAG CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	517
1187	GGCUGAG CUGAUGAGGCCGAAAGGCCGAA AAGGGAC	518
1188	CUGCCCU CUGAUGAGGCCGAAAGGCCGAA AUGGUAA	519
1198	UCAGACU CUGAUGAGGCCGAAAGGCCGAA AACUCCC	520
1209	GAAGGUG CUGAUGAGGCCGAAAGGCCGAA AGGGCUG	521
1215	CGGUGCU CUGAUGAGGCCGAAAGGCCGAA AGGCCAG	522
1229	GCUGAGG CUGAUGAGGCCGAAAGGCCGAA AGGGACC	523
1237	GGGGCAG CUGAUGAGGCCGAAAGGCCGAA AGCUGGG	524
1250	GAGCCUG CUGAUGAGGCCGAAAGGCCGAA AGGCUGG	525
1268	GGGGCAG CUGAUGAGGCCGAAAGGCCGAA AGCUGGG	526
1279	AGGAAGG CUGAUGAGGCCGAAAGGCCGAA ACCAUGG	527
1281	CGCAGCU CUGAUGAGGCCGAAAGGCCGAA AGCCCAC	528
1286	UGGGGGA CUGAUGAGGCCGAAAGGCCGAA AACUCAU	529
1309	AGACUCG CUGAUGAGGCCGAAAGGCCGAA ACAGGAG	530
1315	GGGUUAG CUGAUGAGGCCGAAAGGCCGAA ACUGGGG	531
1318	CCGGGGU CUGAUGAGGCCGAAAGGCCGAA AGAACUG	532
1331	GACUGGG CUGAUGAGGCCGAAAGGCCGAA AGGACCC	533
1334	UCAGCUU CUGAUGAGGCCGAAAGGCCGAA AGAAAAG	534
1389	GGCUUCC CUGAUGAGGCCGAAAGGCCGAA ACAGCGU	535
1413	AGCAUCA CUGAUGAGGCCGAAAGGCCGAA ACUGCAG	536
1414	CAGCAUC CUGAUGAGGCCGAAAGGCCGAA AACUGCA	537
1437	GCCAAGC CUGAUGAGGCCGAAAGGCCGAA AGGCCCC	538
1441	UGUUGCC CUGAUGAGGCCGAAAGGCCGAA AGCAAGG	539
1467	GUCUGUG CUGAUGAGGCCGAAAGGCCGAA ACACUCC	540
1468	GGUCUGU CUGAUGAGGCCGAAAGGCCGAA AACACUC	541
1482	GUCCACA CUGAUGAGGCCGAAAGGCCGAA AUGCCAG	542
1486	AGUUCCC CUGAUGAGGCCGAAAGGCCGAA ACCGAAG	543
1494	AAACUCU CUGAUGAGGCCGAAAGGCCGAA AGUUGUC	544
1500	CUGCUGA CUGAUGAGGCCGAAAGGCCGAA ACUCUGA	545
1501	GCUGCUG CUGAUGAGGCCGAAAGGCCGAA AACUCUG	546
1502	AGCUGCU CUGAUGAGGCCGAAAGGCCGAA AAACUCU	547
1525	ACACAGG CUGAUGAGGCCGAAAGGCCGAA AUGCACC	548

1566	UUCAGGG CUGAUGAGGCCGAAAGGCCGAA ACUCCAU	549
1577	CGAGUUA CUGAUGAGGCCGAAAGGCCGAA AGCUUCA	550
1579	GGCGAGU CUGAUGAGGCCGAAAGGCCGAA AUAGCUU	551
1583	ACCAGGC CUGAUGAGGCCGAAAGGCCGAA AGUUAUA	552
1588	CCCUCUC CUGAUGAGGCCGAAAGGCCGAA AGGAGAG	553
1622	GGGGCAG CUGAUGAGGCCGAAAGGCCGAA AGCUGGG	554
1628	CCUACCG CUGAUGAGGCCGAAAGGCCGAA AGCAGGA	555
1648	CAUUGGG CUGAUGAGGCCGAAAGGCCGAA AGCCCCG	556
1660	CUGGGCA CUGAUGAGGCCGAAAGGCCGAA AGGUCAG	557
1663	CACCUGG CUGAUGAGGCCGAAAGGCCGAA AGCAGAG	558
1664	UCACCUG CUGAUGAGGCCGAAAGGCCGAA AAGCAGA	559
1665	ACCUCCG CUGAUGAGGCCGAAAGGCCGAA AAGCGAG	560
1680	GGAGGAG CUGAUGAGGCCGAAAGGCCGAA AGUCUUC	561
1681	UGGAGGA CUGAUGAGGCCGAAAGGCCGAA AAGUCUU	562
1683	AAUGGAG CUGAUGAGGCCGAAAGGCCGAA AGAAGUC	563
1686	CGCAAUG CUGAUGAGGCCGAAAGGCCGAA AGGAGAA	564
1690	UGUCCGC CUGAUGAGGCCGAAAGGCCGAA AUGGAGG	565
1704	AGCAGAG CUGAUGAGGCCGAAAGGCCGAA AGUCCAU	566
1705	GAGCAGA CUGAUGAGGCCGAAAGGCCGAA AAGUCCA	567
1707	AAGAGCA CUGAUGAGGCCGAAAGGCCGAA AGAAGUC	568
1721	CUGAUCU CUGAUGAGGCCGAAAGGCCGAA ACUCAAA	569
1726	AGGAGCU CUGAUGAGGCCGAAAGGCCGAA AUCUGAC	570
1731	ACCUUAG CUGAUGAGGCCGAAAGGCCGAA AGCUGAU	571
1734	AGCACCU CUGAUGAGGCCGAAAGGCCGAA AGGAGCU	572
1754	CUCUUGG CUGAUGAGGCCGAAAGGCCGAA AGCACUG	573

Table V

Human *rel A* HH Ribozyme Sequences

nt. Sequence	HH Ribozyme Sequence	SEQ ID NO.
19	UACAGAC CUGAUGAGGCCGAAAGGCCGAA AGCCAUU	574
22	CACUACA CUGAUGAGGCCGAAAGGCCGAA ACGAGCC	575
26	CGUGCAC CUGAUGAGGCCGAAAGGCCGAA ACAGACG	576
93	GAGGGGG CUGAUGAGGCCGAAAGGCCGAA ACAGUUC	577
94	UGAGGGG CUGAUGAGGCCGAAAGGCCGAA AACAGUU	578
100	GGAAGAU CUGAUGAGGCCGAAAGGCCGAA AGGGGGA	579
103	CCGGGAA CUGAUGAGGCCGAAAGGCCGAA AUGAGGG	580
105	UGCCGGG CUGAUGAGGCCGAAAGGCCGAA AGAUGAG	581
106	CUGCCGG CUGAUGAGGCCGAAAGGCCGAA AAGAUGA	582
129	GGGGCCA CUGAUGAGGCCGAAAGGCCGAA AGGCCUG	583
138	CUCCACA CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	584
148	GCUCAAU CUGAUGAGGCCGAAAGGCCGAA AUCUCCA	585
151	GCUGCUC CUGAUGAGGCCGAAAGGCCGAA AUGAUCU	586
180	GUAGCGG CUGAUGAGGCCGAAAGGCCGAA AGCGCAU	587
181	UGUAGCG CUGAUGAGGCCGAAAGGCCGAA AAGCGCA	588
186	GCACUUG CUGAUGAGGCCGAAAGGCCGAA AGCGGAA	589
204	GCCCGCG CUGAUGAGGCCGAAAGGCCGAA AGCGCCC	590
217	CGCCUGG CUGAUGAGGCCGAAAGGCCGAA AUGCUGC	591
239	UUGGUGG CUGAUGAGGCCGAAAGGCCGAA AUCUGUG	592
262	UGAUCUU CUGAUGAGGCCGAAAGGCCGAA AUGGUGG	593
268	AGCCAUU CUGAUGAGGCCGAAAGGCCGAA AUCUUGA	594
276	UCCUGUG CUGAUGAGGCCGAAAGGCCGAA AGCCAUU	595
301	CCAGGGA CUGAUGAGGCCGAAAGGCCGAA AUGCGCA	596
303	GACCAGG CUGAUGAGGCCGAAAGGCCGAA AGAUGCG	597
310	CCUUGGU CUGAUGAGGCCGAAAGGCCGAA ACCAGGG	598
323	CGGUGAG CUGAUGAGGCCGAAAGGCCGAA AGGGUCC	599
326	GGCCGGU CUGAUGAGGCCGAAAGGCCGAA AGGAGGG	600
335	UGGGGGU CUGAUGAGGCCGAAAGGCCGAA AGGCCGG	601
349	UUCCUAC CUGAUGAGGCCGAAAGGCCGAA AGCUCGU	602
352	CCUUUCC CUGAUGAGGCCGAAAGGCCGAA ACAAGCU	603
375	CUCAUAG CUGAUGAGGCCGAAAGGCCGAA AGCCAUC	604
376	CCUCAUA CUGAUGAGGCCGAAAGGCCGAA AAGCCAU	605
378	AGCCUCA CUGAUGAGGCCGAAAGGCCGAA AGAAGCC	606
391	CCGGGCA CUGAUGAGGCCGAAAGGCCGAA AGCUCAG	607
409	AACUGUG CUGAUGAGGCCGAAAGGCCGAA AUGCAGC	608
416	UUCUGGA CUGAUGAGGCCGAAAGGCCGAA ACUGUGG	609
417	GUUCUGG CUGAUGAGGCCGAAAGGCCGAA AACUGUG	610
418	GGUUCUG CUGAUGAGGCCGAAAGGCCGAA AAACUGU	611
433	CACACUG CUGAUGAGGCCGAAAGGCCGAA AUUCCCA	612
467	UGACUGA CUGAUGAGGCCGAAAGGCCGAA AGCCUGC	613
469	GCUGACU CUGAUGAGGCCGAAAGGCCGAA AUAGCCU	614
473	AUGCGCU CUGAUGAGGCCGAAAGGCCGAA ACUGAUA	615
481	UGGUCUG CUGAUGAGGCCGAAAGGCCGAA AUGCGCU	616
501	AACUUGG CUGAUGAGGCCGAAAGGCCGAA AGGGGUU	617
502	GAACUUG CUGAUGAGGCCGAAAGGCCGAA AAGGGGU	618
508	CUAUAGG CUGAUGAGGCCGAAAGGCCGAA ACUUGAA	619
509	UCUAUAG CUGAUGAGGCCGAAAGGCCGAA AACUUGG	620
512	UCUUCUA CUGAUGAGGCCGAAAGGCCGAA AGGAACU	621
514	GCUCUUC CUGAUGAGGCCGAAAGGCCGAA AUAGGAA	622
534	CAGGUCG CUGAUGAGGCCGAAAGGCCGAA AGUCCCC	623
556	GGAAGCA CUGAUGAGGCCGAAAGGCCGAA AGCCGCA	624
561	CACCUGG CUGAUGAGGCCGAAAGGCCGAA AGCAGAG	625

562	UCACCUG CUGAUGAGGCCGAAAGGCCGAA AAGCAGA	626
585	CCUGCCU CUGAUGAGGCCGAAAGGCCGAA AUGGGUC	627
598	GCAGGCG CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	628
613	GAGGAAG CUGAUGAGGCCGAAAGGCCGAA ACAGGCG	629
616	GAUGAGG CUGAUGAGGCCGAAAGGCCGAA AGGACAG	630
617	GGAUGAG CUGAUGAGGCCGAAAGGCCGAA AAGGACA	631
620	AUGGGAU CUGAUGAGGCCGAAAGGCCGAA AGGAAGG	632
623	AAGAUGG CUGAUGAGGCCGAAAGGCCGAA AUGAGGA	633
628	UGUCAAA CUGAUGAGGCCGAAAGGCCGAA AUCGGAU	634
630	AUUGUCA CUGAUGAGGCCGAAAGGCCGAA AGAUGGG	635
631	GAUUGUC CUGAUGAGGCCGAAAGGCCGAA AAGAUGG	636
638	GGGGCAC CUGAUGAGGCCGAAAGGCCGAA AUUGUCA	637
661	AGAUCUU CUGAUGAGGCCGAAAGGCCGAA AGCUCGG	638
667	CUCGGCA CUGAUGAGGCCGAAAGGCCGAA AUCUUGA	639
687	GCUGCCA CUGAUGAGGCCGAAAGGCCGAA AGUUUCG	640
700	CCCCACC CUGAUGAGGCCGAAAGGCCGAA AGGCAGC	641
715	GUAGGAA CUGAUGAGGCCGAAAGGCCGAA AUCUCAU	642
717	CAGUAAG CUGAUGAGGCCGAAAGGCCGAA AGAUCUC	643
718	ACAGUAG CUGAUGAGGCCGAAAGGCCGAA AAGAUCU	644
721	CACACAG CUGAUGAGGCCGAAAGGCCGAA AGGAAGA	645
751	ACACCUC CUGAUGAGGCCGAAAGGCCGAA AUGUCCU	646
759	CGUGAAA CUGAUGAGGCCGAAAGGCCGAA ACACCUC	647
761	CCCGUGA CUGAUGAGGCCGAAAGGCCGAA AUACACC	648
762	UCCCGUG CUGAUGAGGCCGAAAGGCCGAA AAUACAC	649
763	GUCCCGU CUGAUGAGGCCGAAAGGCCGAA AAAUACA	650
792	CGAAAAG CUGAUGAGGCCGAAAGGCCGAA AGCCUCG	651
795	UUGCGAA CUGAUGAGGCCGAAAGGCCGAA AGGAGCC	652
796	CUUGCGA CUGAUGAGGCCGAAAGGCCGAA AAGGAGC	653
797	GCUUGCG CUGAUGAGGCCGAAAGGCCGAA AAAGGAG	654
798	AGCUUGC CUGAUGAGGCCGAAAGGCCGAA AAAAGGA	655
829	GGAACAC CUGAUGAGGCCGAAAGGCCGAA AUGGCCA	656
834	GGUCCGG CUGAUGAGGCCGAAAGGCCGAA ACACAAU	657
835	GGGUCCG CUGAUGAGGCCGAAAGGCCGAA AACACAA	658
845	GCGUAGG CUGAUGAGGCCGAAAGGCCGAA AGGGGUC	659
849	GUCUGCG CUGAUGAGGCCGAAAGGCCGAA AGGGAGG	660
872	CGCACAG CUGAUGAGGCCGAAAGGCCGAA AGCCUGC	661
883	GCAUGGA CUGAUGAGGCCGAAAGGCCGAA ACACGCA	662
885	CUGCAUG CUGAUGAGGCCGAAAGGCCGAA AGACACG	662
905	CGGUCGG CUGAUGAGGCCGAAAGGCCGAA AGGCCGC	664
906	CCGGUCG CUGAUGAGGCCGAAAGGCCGAA AAGGCCG	665
919	GCUCACU CUGAUGAGGCCGAAAGGCCGAA AGCUCCC	666
936	GUACUGG CUGAUGAGGCCGAAAGGCCGAA AUUCCAU	667
937	GGUACUG CUGAUGAGGCCGAAAGGCCGAA AAUUCCA	668
942	UGGCAGG CUGAUGAGGCCGAAAGGCCGAA ACUGGAA	669
953	UCGUCUG CUGAUGAGGCCGAAAGGCCGAA AUCUGGC	670
962	CGGUGAC CUGAUGAGGCCGAAAGGCCGAA AUCGUCU	671
965	AUCCGGU CUGAUGAGGCCGAAAGGCCGAA ACGAUCG	672
973	UCUCCUC CUGAUGAGGCCGAAAGGCCGAA AUCCGGU	673
986	GUCCUUU CUGAUGAGGCCGAAAGGCCGAA AGGUUUC	674
996	GGUCUCA CUGAUGAGGCCGAAAGGCCGAA AUGUCCU	675
1005	GCUCUUG CUGAUGAGGCCGAAAGGCCGAA AGGUCUC	676
1006	UGCUCUU CUGAUGAGGCCGAAAGGCCGAA AAGGUCU	677
1015	UCUUCAU CUGAUGAGGCCGAAAGGCCGAA AUGCUCU	678
1028	CUGAAAG CUGAUGAGGCCGAAAGGCCGAA ACUCUUC	679
1031	CCGCUGA CUGAUGAGGCCGAAAGGCCGAA AGGACUC	680
1032	UCCGCUG CUGAUGAGGCCGAAAGGCCGAA AAGGACU	681
1033	GUCCGCU CUGAUGAGGCCGAAAGGCCGAA AAAGGAC	682

1058	CGAGGUG CUGAUGAGGCCGAAAGGCCGAA AGGCCGG	683
1064	AUGCGUC CUGAUGAGGCCGAAAGGCCGAA AGGUGGA	684
1072	GCACAGC CUGAUGAGGCCGAAAGGCCGAA AUGCGUC	685
1082	CUGCGGG CUGAUGAGGCCGAAAGGCCGAA AGGCACA	686
1083	GCUGCGG CUGAUGAGGCCGAAAGGCCGAA AAGGCAC	687
1092	AGAAGCU CUGAUGAGGCCGAAAGGCCGAA AGCUGCG	688
1097	GGGACAG CUGAUGAGGCCGAAAGGCCGAA AGCUGAG	689
1098	GGGGACA CUGAUGAGGCCGAAAGGCCGAA AAGCUGA	690
1102	GCUUGGG CUGAUGAGGCCGAAAGGCCGAA ACAGAAG	691
1125	AAAGGGA CUGAUGAGGCCGAAAGGCCGAA AGGGCUG	692
1127	GUAAAGG CUGAUGAGGCCGAAAGGCCGAA AUAGGGC	693
1131	UGACGUA CUGAUGAGGCCGAAAGGCCGAA AGGGAUA	694
1132	AUGACGU CUGAUGAGGCCGAAAGGCCGAA AAGGGAU	695
1133	GAUGACG CUGAUGAGGCCGAAAGGCCGAA AAAGGGA	696
1137	CAGGGAU CUGAUGAGGCCGAAAGGCCGAA ACGUAAA	697
1140	GCUCAGG CUGAUGAGGCCGAAAGGCCGAA AUGACGU	698
1153	CAUAGUU CUGAUGAGGCCGAAAGGCCGAA AUGGUGC	699
1158	CUCAUCA CUGAUGAGGCCGAAAGGCCGAA AGUUGAU	700
1167	GGUGGGA CUGAUGAGGCCGAAAGGCCGAA ACUCAUC	701
1168	UGGUGGG CUGAUGAGGCCGAAAGGCCGAA AACUCAU	702
1169	AUGGUGG CUGAUGAGGCCGAAAGGCCGAA AAACUCA	703
1182	AGAAGGA CUGAUGAGGCCGAAAGGCCGAA ACACCAU	704
1183	CAGAAGG CUGAUGAGGCCGAAAGGCCGAA AACACCA	705
1184	CCAGAAG CUGAUGAGGCCGAAAGGCCGAA AAACACC	706
1187	UGCCCAG CUGAUGAGGCCGAAAGGCCGAA AAGAAAC	707
1188	CUGCCCA CUGAUGAGGCCGAAAGGCCGAA AAGGAAA	708
1198	CCUGGCU CUGAUGAGGCCGAAAGGCCGAA AUCUGCC	709
1209	GAAGGCC CUGAUGAGGCCGAAAGGCCGAA AGGCCUG	710
1215	CGGGGCC CUGAUGAGGCCGAAAGGCCGAA AGGCCGA	711
1229	ACUUGGG CUGAUGAGGCCGAAAGGCCGAA AGGGGCC	712
1237	GGGGCAG CUGAUGAGGCCGAAAGGCCGAA ACUUGGG	713
1250	GGGGCUG CUGAUGAGGCCGAAAGGCCGAA AGCCUGG	714
1268	AUGGCUG CUGAUGAGGCCGAAAGGCCGAA AGCAGGG	715
1279	GAGCUGA CUGAUGAGGCCGAAAGGCCGAA ACCAUGG	716
1281	CAGAGCU CUGAUGAGGCCGAAAGGCCGAA AUACCAU	717
1286	UGGGCCA CUGAUGAGGCCGAAAGGCCGAA AGCUGAU	718
1309	GGACUGG CUGAUGAGGCCGAAAGGCCGAA ACAGGGG	719
1315	GGGCUAG CUGAUGAGGCCGAAAGGCCGAA ACUGGGA	720
1318	CUGGGGC CUGAUGAGGCCGAAAGGCCGAA AGGACUG	721
1331	GCCUGAG CUGAUGAGGCCGAAAGGCCGAA AGGGCCU	722
1334	ACAGCCU CUGAUGAGGCCGAAAGGCCGAA AGGAGGG	723
1389	GGCCUCU CUGAUGAGGCCGAAAGGCCGAA ACAGCGU	724
1413	AUCAUCA CUGAUGAGGCCGAAAGGCCGAA ACUGCAG	725
1414	CAUCAUC CUGAUGAGGCCGAAAGGCCGAA AACUGCA	726
1437	GCCAAGC CUGAUGAGGCCGAAAGGCCGAA AGGCCCC	727
1441	UGUUGCC CUGAUGAGGCCGAAAGGCCGAA AGCAAGG	728
1467	GUCUGUG CUGAUGAGGCCGAAAGGCCGAA ACACAGC	729
1468	GGUCUGU CUGAUGAGGCCGAAAGGCCGAA AACACAG	730
1482	GUCGACG CUGAUGAGGCCGAAAGGCCGAA AUGCCAG	731
1486	AGUUGUC CUGAUGAGGCCGAAAGGCCGAA ACGGAUG	732
1494	AAACUCG CUGAUGAGGCCGAAAGGCCGAA AGUUGUC	733
1500	CUGCUGA CUGAUGAGGCCGAAAGGCCGAA ACUCGGA	734
1501	GCUGCUG CUGAUGAGGCCGAAAGGCCGAA AACUCGG	735
1502	AGCUGCU CUGAUGAGGCCGAAAGGCCGAA AAACUCG	736
1525	CCACAGG CUGAUGAGGCCGAAAGGCCGAA AUGCCCU	737
1566	CUCAGGG CUGAUGAGGCCGAAAGGCCGAA ACUCCAU	738
1577	CGAGUUA CUGAUGAGGCCGAAAGGCCGAA AGCCUCA	739

1579	GGCGAGU CUGAUGAGGCCGAAAGGCCGAA AUAGCCU	740
1583	ACCAGGC CUGAUGAGGCCGAAAGGCCGAA AGUUAUA	741
1588	CUGUCAC CUGAUGAGGCCGAAAGGCCGAA AGGCGAG	742
1622	GGAGCAG CUGAUGAGGCCGAAAGGCCGAA AGCUGGG	743
1628	CCCAGUG CUGAUGAGGCCGAAAGGCCGAA AGCAGGA	744
1648	CAUUGGG CUGAUGAGGCCGAAAGGCCGAA AGCCCCG	745
1660	CUGAAAG CUGAUGAGGCCGAAAGGCCGAA AGGCCAU	746
1663	CUCCUGA CUGAUGAGGCCGAAAGGCCGAA AGGAGGC	747
1664	UCUCCUG CUGAUGAGGCCGAAAGGCCGAA AAGGAGG	748
1665	AUCUCCU CUGAUGAGGCCGAAAGGCCGAA AAAGGAG	749
1680	GGAGGAG CUGAUGAGGCCGAAAGGCCGAA AGUCUUC	750
1681	UGGAGGA CUGAUGAGGCCGAAAGGCCGAA AAGUCUU	751
1683	AAUGGAG CUGAUGAGGCCGAAAGGCCGAA AGAAGUC	752
1686	CGCAAUG CUGAUGAGGCCGAAAGGCCGAA AGGAGAA	753
1690	UGUCCGC CUGAUGAGGCCGAAAGGCCGAA AUGGAGG	754
1704	GGCUGAG CUGAUGAGGCCGAAAGGCCGAA AGUCCAU	755
1705	GGGCUGA CUGAUGAGGCCGAAAGGCCGAA AAGUCCA	756
1707	CAGGGCU CUGAUGAGGCCGAAAGGCCGAA AGAAGUC	757
1721	CUGAUCU CUGAUGAGGCCGAAAGGCCGAA ACUCAGC	758
1726	AGGAGCU CUGAUGAGGCCGAAAGGCCGAA AUCUGAC	759
1731	CCCUUAG CUGAUGAGGCCGAAAGGCCGAA AGCUGAU	760
1734	ACCCCCU CUGAUGAGGCCGAAAGGCCGAA AGGAGCU	761
1754	CUCUGGG CUGAUGAGGCCGAAAGGCCGAA AGGGCAG	762

Table VI
Human *rel A* Hairpin Ribozyme/Target Sequences

nt. Position	Hairpin Ribozyme sequence	Seq ID No.	Substrate	Seq ID No.
90	UGAGGGGG AGAA GUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	763	GAACU GUU CCCCCUCA	778
156	GCUGCUUG AGAA GCUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	764	GAGCA GCC CAAGCAGC	779
362	GCCAUCCC AGAA GUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	765	GGACU GCC GGGAUGGC	780
413	GUUCUGGA AGAA GUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	766	CCACA GUU UCCAGAAC	781
606	GAAGGACA AGAA GCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	767	CUGCC GCC UGUCCUUC	782
652	UUGAGCUC AGAA GUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	768	ACACU GCC GAGCUCAA	783
695	CCCACCGA AGAA GCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	769	CAGCU GCC UCGGUGGG	784
853	AGGCUGGG AGAA GCGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	770	ACGCA GAC CCCAGCCU	785
900	GGUCGGAA AGAA GCCG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	771	CGGCG GCC UUCCGACC	786
955	UGACGAUC AGAA GUAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	772	AUACA GAC GAUCGUCA	787
1037	GUCGGUGG AGAA GCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	773	CAGCG GAC CCACCGAC	788
1045	GGCCGGGG AGAA GUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	774	CCACC GAC CCCCGGCC	789
1410	CAUCAUCA AGAA GCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	775	CUGCA GUU UGAUGAUG	790
1453	ACAGCUGG AGAA GUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	776	GCACA GAC CCAGCUGU	791
1471	GAUGCCAG AGAA GUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	777	UCACA GAC CUGGCAUC	792

Table VII

Mouse *rel A* Hairpin Ribozyme/Target Sequences

nt. Position	Hairpin Ribozyme sequence	Seq. ID No.	Substrate	Seq. ID No.
137	GUUGCUUC AGAA GUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	793	GAACA GCC GAAGCAAC	812
273	GAGAUUCG AGAA GUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	794	GAACA GUU CGAAUCUC	813
343	GCCAUCCC AGAA GUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	795	GGACU GCC GGGAUGGC	814
366	GGGCAGAG AGAA GCCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	796	AGGCU GAC CUCUGCCC	815
633	UUGAGCUC AGAA GUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	797	ACACU GCC GAGCUCAA	816
676	CCCACCGA AGAA GCUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	798	GAGCU GCC UCGGUGGG	817
834	AGGCUGGG AGAA GCGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	799	ACGCC GAC CCCAGCCU	818
881	GAUCAGAA AGAA GCCG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	800	CGGCG GCC UUCUGAUC	819
1100	AGGUGUAG AGAA GCGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	801	CCGCA GCC CUACACCU	820
1205	GGGCAGAG AGAA GUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	802	GCACC GUC CUCUGCCC	821
1361	GGGCUUCC AGAA GCGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	803	ACGCU GUC GGAAGCCC	822
1385	CAGCAUCA AGAA GCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	804	CUGCA GUU UGAUGCUG	823
1431	ACUCCUGG AGAA GUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	805	GCACA GAC CCAGGAGU	824
1449	GAUGCCAG AGAA GUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	806	UCACA GAC CUGGCAUC	825
1802	AAGUCGGG AGAA GCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	807	CAGCU GCC CCCGACUU	826
2009	UGGCUCCA AGAA GUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	808	GGACA GAC UGGAGCCA	827
2124	UGGUGUCG AGAA GCAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	809	GUGCU GCC CGACACCA	828
2233	AUUCUGAA AGAA GCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	810	UGGCC GCC UUCAGAAU	829
2354	UCAGUAAA AGAA GUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	811	AGACA GCC UUUACUGA	830